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SHORT-TERM MEMORY IS INDEPENDENT OF BRAIN PROTEIN SYNTHESIS

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Running Title: Protein Synthesis and Short-Term Memory

Abstract

Male Swiss albino CD-1 mice given a single injection of a cerebral protein synthesis inhibitor, anisomycin (ANI) (1 mg/animal), 20 min prior to single trial passive avoidance training demonstrated impaired retention at tests given 3 hr, 6 hr, 1 day, and 7 days after training. Retention was not significantly different from saline controls when tests were given 0.5 or 1.5 hr after training. Prolonging inhibition of brain protein synthesis by giving either 1 or 2 additional injections of ANI 2 or 2 and 4 hr after training did not prolong short-term retention performance. The temporal development of impaired retention in ANI treated mice could not be accounted for by drug dosage, duration of protein synthesis inhibition, or nonspecific sickness at test. In contrast to the suggestion that protein synthesis inhibition prolongs short-term memory (Quinton, 1978), the results of this experiment indicate that short-term memory is not prolonged by antibiotic drugs that inhibit cerebral protein synthesis. All evidence seems consistent with the hypothesis that short-term memory is protein synthesis independent and that the establishment of long-term memory depends upon protein synthesis during or shortly after training. Evidence for a role of protein synthesis in memory maintenance is discussed.

Short-Term Memory is Independent of Brain Protein Synthesis

Inhibition of cerebral protein synthesis shortly before or after training markedly impairs long-term retention in a variety of tasks and species (Agranoff, 1971; Barondes, 1975; Barraco & Stettner, 1976; Flexner, Flexner, & Stellar, 1967). These findings suggest that cerebral protein synthesis is required for the formation of long-term memory. A cardinal feature of the amnesia induced by protein synthesis inhibitors (PSIs) is that there is no effect on either acquisition (Cohen & Barondes, 1968; Flood, Bennett, Orme, & Rosenzweig, 1975a; Gibbs & Ng, 1977; Squire & Barondes, 1974) or short-term memory (Barondes & Cohen, 1967; Davis, Spanis, & Squire, 1976; Gibbs & Ng, 1977; Watts & Mark, 1970). This feature of PSI-induced amnesia has been taken as evidence that short-term memory is a distinct biological entity that does not depend on cerebral protein synthesis (Barondes, 1975; Flood & Jarvik, 1976; Squire, 1975), and this has led to numerous studies designed to characterize the temporal course and neural substrate of short-term memory. However, the basic conclusion that short-term memory is unaffected by inhibition of brain protein synthesis has been challenged by two findings in the literature. The first of these was based on reports that the PSI cycloheximide (CYC) disrupts short-term memory (Gutwein, Quartermain, & McEwen, 1974; Quartermain & McEwen, 1970; Rainbow, Adler, & Flexner, 1976; Randt, Barnett, McEwen, & Quartermain, 1971). The second was based on a report that CYC prolongs short-term memory (Quinton, 1978).

The suggestion that PSIs disrupt short-term memory was based on reports that mice subcutaneously injected with CYC before training in a one-trial step-through passive avoidance task exhibited impaired retention minutes after training (Gutwein et al., 1974; Quartermain & McEwen, 1970; Rainbow et al., 1976; Randt et al., 1971). These findings have been evaluated previously by comparing the effects on short-term memory of intracerebral or subcutaneous injection of two PSIs, CYC and anisomycin (ANI) (Davis et al., 1976). Subcutaneously injected CYC produced impaired performance at short training-test intervals, but establishment of protein synthesis inhibition by ANI or by intracerebrally injected CYC did not impair performance at the same intervals after training. These results along with reports that subcutaneous injections of CYC result in increased locomotor activity (Segal, Squire, & Barondes, 1971), an effect not shared by ANI or intracerebrally injected CYC, led the authors to conclude that the "impaired short-term memory" of CYC treated mice was likely due to increased locomotor activity and further, that CYC-induced disruption of performance of the passive avoidance habit at short training-test intervals is not support for the view that short-term memory is impaired by the PSIs. This conclusion is made even more compelling by numerous reports demonstrating that subcutaneous CYC does not impair short-term retention in tasks like active avoidance and discrimination learning (Barraco & Stettner, 1976), where changes in locomotor activity are less likely to confound the measure of performance.

In the present experiment, we have addressed the possibility suggested by Quinton (1978) that the PSIs prolong short-term memory. This suggestion was based on the finding that a nonamnestic dose of CYC (30 mg/kg) given immediately after training renders memory susceptible to disruption by a second injection of CYC (30 mg/kg) or to a carbon dioxide treatment for an unusually

long time after training. The first nonamnestic dose of CYC (or other PSI) was thought to suppress cerebral metabolism during a critical time after training so as to retard long-term memory formation and prolong short-term memory. If another PSI treatment is administered during reduced metabolism, long-term memory formation would be further delayed and short-term memory extended. This possibility was inferred from retention tests given 72 hr after training. Here we evaluate directly the possibility that protein synthesis inhibition affects short-term memory by measuring how long memory persists after training. We have assumed that if short-term memory is extended by post-training injections of a PSI, then such short-term memory should be capable of supporting performance for an extended time after training. Thus, we examine the course of forgetting of the passive avoidance habit as a function of different durations of post-training inhibition of protein synthesis.

Experiment 1

In this experiment we examined the time course of forgetting following a single pretraining injection of either ANI (1 mg/animal) or physiological saline solution.

Method

Subjects. Male Swiss-Webster CD-1 mice were obtained from Charles Rivers Breeding Laboratories at 55 days of age. Animals were housed 5 to a cage until approximately 48 hr prior to training. Mice were then housed

individually and remained so throughout the experiment. Ad lib access to food and water was provided.

Apparatus and procedure. Mice were given one-trial passive avoidance training in a step-through apparatus described previously (Flood, Bennett, Rosenzweig, & Orme, 1972). A black Plexiglas panel with a 3.8 cm dia. hole at its base separated a black Plexiglas start box (9 cm long x 10.2 cm wide x 12.5 cm high) from a white Plexiglas shock compartment (35 cm long x 8.2 cm wide x 12.5 cm high). The apparatus was illuminated by a 1.8 W light bulb situated behind a white translucent panel at the end of the shock compartment. A guillotine door consisting of translucent white Plexiglas blocked access to the shock compartment prior to training. A 0.25 mA shock was delivered through 2.4 mm dia. brass rods in the shock compartment by a constant current shock scrambler. The apparatus was cleaned with alcohol and allowed to dry before the testing of each animal.

For training, a mouse was placed into the dark start box for 10 sec after which the light illuminating the apparatus was turned on. After a minimum of an additional 10 sec the guillotine door was removed when the mouse was oriented away from the entrance. The step-through latency (STL) was measured as the time from orientation to the entrance until the mouse had all four paws on the grid. Five seconds later a continuous 0.25 mA footshock was delivered until the mouse escaped back into the start box. The guillotine door was replaced, the light was turned off, and approximately 5 sec later the mouse was returned to its home cage. Animals having STLs greater than 20 sec or escape latencies greater than 12 sec were removed from the experiment (Out of 321 trained, a total of 17 were removed). Testing was identical to training

except that no footshock was administered. Animals not entering the shock compartment within 300 sec were removed and given a test score of 300. Overall effect of drug treatment was evaluated with the Kruskal-Wallis one-way analysis of variance. The STLs for different treatment groups tested at the same time were compared with the Kolmogorov-Smirnov two-sample test. Mice were tested for retention either 0.5 hr, 1.5 hr, 3 hr, 6 hr, 1 day, or 7 days after training.

Drug. ANI (2-p-methoxyphenyl-3-acetoxy-4-hydroxypyrollidine), obtained from the Pfizer Pharmaceutical Company, was dissolved in saline by adding an approximately equal molar amount of 3 N HCl and adjusting the pH to 6-7 with NaOH. Subcutaneous injections of saline or the saline solution containing ANI (4 mg/ml) were made on the back of mice 20 min prior to training, in a volume of 0.25 ml.

Results

Mice that received a subcutaneous injection of ANI (1 mg/animal) or saline demonstrated similar STLs for training. The mean STLs were 6.6 ± 0.3 and 7.1 ± 0.4 respectively, and a one-way analysis of variance demonstrated no measurable effect on training STLs, $F(1,302)=0.84$, $p > 0.35$. There was, however, a highly significant drug effect on escape latencies, $F(1,302)=22.8$, $p<0.001$. The mean escape latencies for ANI and saline treated mice were 7.3 ± 0.4 and 4.9 ± 0.3, respectively. This difference cannot account for ANI-induced amnesia since it has previously been demonstrated that an increase in escape latencies results in greater training strength (Flood et al., 1972);

this would predict better retention for ANI treated mice, but this was not the case.

Median STLs achieved at retention test for saline and ANI treated mice are given in Table 1. Mice injected with ANI demonstrated retention equivalent to saline injected mice at retention tests given 0.5 and 1.5 hr after training. However, ANI-treated mice showed significantly impaired performance at all subsequent test times (3 hr, 6 hr, 1 day, 7 days) as compared to saline treated mice (see Table 1).

(Insert Table 1 about here)

The training-test interval exerted a significant effect on the performance of both ANI-treated ($H=17.9$, $df=5$, $p<0.01$) and saline-treated ($H=25.8$, $df=5$, $p<0.001$) mice as revealed by a Kruskal-Wallis one-way analysis of variance. ANI treated mice tested 0.5 and 1.5 hr after training demonstrated significantly better retention than similarly treated mice tested at 6 hr, 1 day, or 7 days after training with one exception; the comparison between mice tested at 0.5 hr and 1 day only approached statistical significance (two-tailed $p<0.08$). Post-hoc analysis indicated no difference in retention for ANI treated mice tested 3 hr, 6 hr, 1 day, or 7 days after training. Likewise, there was no significant difference between mice treated with ANI and tested 0.5, 1.5, or 3 hr after training. Saline-treated mice demonstrated similar retention when tested 3 hr, 6 hr, 1 day, or 7 days after training. Analysis of STLs of saline mice tested at 0.5 hr as compared to saline treated mice tested at 3 hr, 6 hr, and 1 day indicated poorer performance by the mice tested at 0.5 hr. Similarly, mice tested at 1.5 hr performed significantly

poorer than controls tested at 6 hr. No significant difference was detected between mice tested at 0.5 and 1.5 hr after training.

Discussion

The results of this experiment confirm our previous report that ANI (1 mg/animal) impairs the long-term retention of the passive-avoidance habit at 1 and 7 days (Davis, Rosenzweig, Bennett, & Orme, 1978). Additionally, retention tests given at shorter training-test intervals indicates that retention of ANI-treated mice is normal for the first 1.5 hr after training but is impaired at tests administered 3 and 6 hr after training. The gradual development of PSI-induced amnesia reported here is consistent with previous studies demonstrating normal retention in PSI-treated animals from minutes to hours after training (Davis et al., 1976; Gibbs & Ng, 1977).

Experiment 2

In this experiment we addressed the possibility that inhibition of brain protein synthesis prolongs short-term memory. If a PSI suppresses cerebral metabolism during a posttraining period and prolongs short-term memory, then it should be possible to demonstrate a prolongation of the short-term phase by prolonging the duration of protein synthesis inhibition. To test this possibility we extended the period of 90% inhibition of brain protein synthesis from 2 hr to 4 hr and even to 6 hr by giving either 1 or 2 additional injections of ANI either 2 hr or 2 and 4 hr after the initial pretraining treatment.

Method

The behavioral apparatus, training, testing, and subjects were the same as in Experiment 1. In order to vary the duration of inhibition of protein synthesis, we gave each mouse one of the following drug treatments: 1) an injection of saline 20 min pretraining and a second injection of saline 2 hr later; 2) an injection of ANI (1 mg/animal) 20 min pretraining and a second injection of ANI (1 mg/animal) 2 hr later; 3) an injection of saline 20 min pretraining and 2 additional injections of saline, each at 2 hr intervals; 4) an injection of ANI (1 mg/animal) 20 min pretraining and 2 additional injections of ANI (1 mg/animal), each at 2 hr intervals. Retention tests were conducted at times when protein synthesis inhibition was > 90% (3 and 6 hr post-training), since this procedure would detect prolongation of short-term memory caused by the inhibition.

Results and Discussion

As in Experiment 1, ANI did not affect training STLs, $F(1,228)=0.61$, $p>0.40$, but did significantly increase escape latencies, $F(1,228)=16.9$, $p<0.001$. However, as noted earlier increased escape latencies by ANI-treated mice cannot account for their poor performance at test.

(Insert Figure 1 about here)

The median STLs obtained at different test times after training are shown in Figure 1. The STL scores obtained in Experiment 1 by the mice that received a single injection of either ANI or saline are included for comparison. Mice receiving either 2 injections of ANI (1 mg/animal/injection) or 3 injections of ANI (1 mg/animal/injection) demonstrated impaired retention at all tests as compared to saline control mice. The training-test interval did not significantly affect retention STLs. That is, within each treatment group performance was similar irrespective of test time. These results indicate that for ANI (1 mg/injection), prolonging inhibition of cerebral protein synthesis does not extend the normal retention demonstrated by mice shortly after training. Retention was impaired at 3 hr irrespective of whether inhibition was greater than 90% for approximately 2 hr (ANI x 1) or was greater than 90% at test and had been so for the previous 3 hr (ANI x 2). Similarly, at 6 hr posttraining, short-term performance was not maintained in mice that received 3 successive injections of ANI even though inhibition greater than 90% had been maintained over the 6 hr in this group.

Determinations of percent inhibition of protein synthesis for the doses and injection schedules of ANI used in this and subsequent experiments have been reported previously (Davis et al., 1978; Flood, Jarvik, Bennett, Orme, & Rosenzweig, 1977). These reports indicate that multiple injections of ANI do not produce a significant cumulative effect -- that is, the inhibition produced by a second and third injection were similar to that of the first if identical dosages of ANI were administered to the mice.

Experiment 3

Quinton (1978) used a subamnesic dose of CYC in demonstrating a prolongation of the amnesic gradient of CO_2. It could be argued that since a single treatment of ANI (1 mg/animal) impairs memory at 3 hr it is not possible to demonstrate prolonged short-term memory with such a high dosage. In this experiment we investigate this possibility by using an initial subamnesic dose of ANI (0.5 mg/animal) and testing retention at various times after training.

Method

Behavioral apparatus, training, testing, and subjects were the same as described in Experiment 1. Mice were administered one of the following drug treatments: 1) a single injection of ANI (0.5 mg/animal) 20 min pretraining; 2) a single injection of saline 20 min pretraining; 3) an injection of ANI (0.5 mg/animal) 20 min pretraining and 2 hr later an injection of ANI (2 mg/animal); 4) an injection of saline 20 min pretraining and a second injection of saline 2 hr later; 5) an injection of ANI (0.5 mg/animal) 20 min pretraining, an injection of ANI (2 mg/animal) 2 hr later, and a third injection of ANI (2 mg/animal) 4 hr after the initial injection; 6) a total of 3 injection of saline at 2 hr intervals with the initial injection 20 min prior to training. Groups were tested for retention at either 3, 6, or 24 hr after training. The choice of a 2 mg/animal dose of ANI was based on pilot work indicating that when the second injection was 1 mg/animal, mice were not amnesic at a 24 hr test.

Results and Discussion

As in experiments 1 and 2, training STLs were unaffected by ANI ($p>0.40$). The difference in escape latencies between ANI and saline treated mice approached significance with the latencies of ANI treated mice tending to be greater, $F(1,158)=3.38$, $p<0.07$. Median STLs demonstrated at retention tests by the different groups are presented in Figure 2. A single injection of ANI (0.5 mg/animal) did not significantly impair retention during tests; memory was as good as that of saline controls at 3 hr and thereafter. However, mice receiving either 1 or 2 additional injections of ANI (2 mg/animal) were impaired at retention tests conducted either 6 or 24 hr after training ($p<0.025$ in all cases). If protein synthesis inhibition were extending short-term memory then it might be expected that mice receiving 2 additional injections of ANI (2 mg/animal) would show normal retention performance at 6 hr, but this was not the case. Instead, mice receiving an initial subamnesic injection of ANI had impaired retention 6 hr after training following either 4 or 6 hr of inhibition of cerebral protein synthesis > 90%. Thus, these findings indicate that the failure to demonstrate a prolongation of short-term memory in Experiment 2 cannot be simply attributed to the drug dosage employed. Further, these results provide additional support for the conclusion that inhibition of brain protein synthesis does not prolong short-term memory.

(Insert Figure 2 about here)

Experiment 4

Two additional possible explanations for the impaired retention of ANI treated mice in Experiments 1 and 2 are 1) a general sickness from drug treatment at test, or 2) that impairment occurs after some particular duration of protein synthesis inhibition. The first possibility, sickness, was examined by initiating inhibition of protein synthesis 1 hr after training. The second possibility, that impairment occurs after some particular duration of inhibition, was examined by initiating inhibition of protein synthesis hours before training.

Method

Behavioral apparatus, training, testing and subjects were the same as in Experiment 1. Mice received one of the following drug treatments: 1) 1, 2, or 3 injections of ANI (1 mg/animal) with the initial injection 1 hr after training and subsequent injections at 2 hr intervals; 2) two injections of ANI (1 mg/animal) or saline with the first being administered 290 min prior to training and the second 170 min prior to training. Mice in the first condition were tested 24 hr after training and mice in the second condition were tested 3 hr after training.

Results and Discussion

Mice receiving either 1, 2, or 3 injections of ANI starting 1 hr after training were not significantly different at test from mice receiving an equivalent number of saline injections and tested 24 hr after training ($p>0.35$, in all cases). The saline mice used for comparison were those from Experiment 1. These results suggest that amnesia cannot be accounted for by nonspecific sickness at test time. Mice that were administered ANI prior to training demonstrated normal retention when tested 3 hr after training ($p>0.90$) as compared to mice that received an identical saline treatment. Thus, memory does not simply decay as a function of duration of protein synthesis inhibition. Instead, inhibition at the time of training must be high in order for ANI to block long-term memory formation.

General Discussion

These experiments indicate that the PSI ANI does not prolong short-term memory. This contrasts with the suggestion of Quinton (1978) that inhibitors of brain protein synthesis decrease cerebral metabolism and thereby prolong short-term memory. The conclusion of this study, that short-term memory is not prolonged by inhibition of brain protein synthesis, was based on direct observations of forgetting as a function of the duration of protein synthesis inhibition. We were able to achieve this by using an inhibitor of protein synthesis with relative few toxic side-effects. In contrast, Quinton's conclusion about prolongation of short-term memory was not based on direct observation of the duration of short-term performance, but instead was inferred

from the observation that CO_2 was an effective amnestic agent for an unusually long time after training if mice were initially treated with a subamnesic dose of CYC. We must therefore conclude that our study provides a more direct test of the hypothesis that the PSIs prolong short-term memory, and that the results do not support such a hypothesis.

While we have reached a different conclusion than Quinton (1978), it is important to note that our results and those of Quinton (1978) are not contradictory. For example, in Experiment 3 mice treated with ANI (2 mg/animal) after an initial subamnesic dose of ANI (0.5 mg/animal) demonstrated impaired retention 6 and 24 hr after training. It is unlikely that the posttraining injection of ANI (2 mg/animal) would produce amnesia without an initial subamnesic pretraining treatment. This conclusion is based on a previous report in which we used the same task, drug, and species, and failed to observe impaired retention in mice given a single posttraining injection of a much higher dose of ANI (7 mg/animal) (Davis et al., 1978). Thus, like Quinton (1978), we find that an amnesic agent can demonstrate an unusually long retroactive gradient following an initial subamnesic perturbation.

Previous studies have reported similar prolonged retroactive influences on memory after various treatments such as pharmacological excitants and depressants (Flood, Jarvik, Bennett, Orme, & Rosenzweig, 1977), hormones (Barondes & Cohen, 1968), PSIs (Flood, Bennett, Rosenzweig, & Orme, 1973), and electroconvulsive shock (Flood, Bennett, Orme, & Jarvik, 1977; Andry & Luttges, 1973) following an initial pretraining injection of a PSI that by itself did not affect retention. Prolongation of susceptiblity to memory disruption by amnesic treatments has also been obtained following initial nonamnesic perturbation by locus coeruleus lesions (Zornetzer, Abraham, & Appleton, 1978) or paradoxical sleep deprivation (Fishbein, McGaugh,

Davis, H. P., Rosenzweig, M. R., Bennett, E. L., & Orme, A. E. Recovery as a function of the degree of amnesia due to protein synthesis inhibition. Pharmacology Biochemistry and Behavior, 1978, 8, 701-710.

Davis, H. P., Spanis, C. W., & Squire, L. R. Inhibition of cerebral protein synthesis: performance at different times after passive avoidance training. Pharmacology Biochemistry and Behavior, 1976, 4, 13-16.

Deutsch, J. A. The cholinergic synapse and the site of memory. Science, 1971, 174, 788-794.

Fishbein, W., McGaugh, J. L., & Swarz, J. R. Retrograde amnesia: electroconvulsive shock effects after termination of rapid eye movement sleep deprivation. Science, 1971, 172, 80-82.

Flexner, J. B., Flexner, L. B., & Stellar, E. Memory in mice as affected by intracerebral puromycin. Science, 1963, 141, 57-59.

Flood, J. F., Bennett, E. L., Orme, A. E., & Jarvik, M. E. Protein synthesis dependent gradient of ECS retrograde amnesia. Behavioral Biology, 1977, 21, 307-328.

Flood, J. F., Bennett, E. L., Orme, A. E., & Rosenzweig, M. R. Effects of protein synthesis inhibition on memory for active avoidance training. Physiology and Behavior, 1975a, 14, 177-184.

Flood, J. F., Bennett, E. L., Orme, A. E., & Rosenzweig, M. R. Relation of memory formation to controlled amounts of brain protein synthesis. Physiology and Behavior, 1975b, 15, 97-102.

Flood, J. F., Bennett, E. L., Rosenzweig, M. R., & Orme, A. E. The influence of training strength on amnesia induced by pre-training injections of cycloheximide. Physiology and Behavior, 1972, 9, 589-600.

Flood, J. F., Bennett, E. L., Rosenzweig, M. R., & Orme, A. E. The influence of duration of protein synthesis inhibition on memory. Physiology and Behavior, 1973, 10, 555-562.

Flood, J. F., & Jarvik, M. E. Drug influences on learning and memory. In M. R. Rosenzweig & E. L. Bennett (Eds.), Neural Mechanisms of Learning and Memory. Cambridge: MIT Press, 1976.

Flood, J. F., Jarvik, M. E., Bennett, E. L., Orme, A. E., & Rosenzweig, M. R. The effects of stimulants, depressants, and protein synthesis inhibition on retention. Behavioral Biology, 1977, 20, 168-183.

Gibbs, M. E., & Ng, K. T. Psychobiology of memory: towards a model of memory formation. Biobehavioral Reviews, 1977, 1, 113-136.

Gutwein, B. M., Quartermain, D., & McEwen, B. S. Dissociation of cycloheximide effects on activity from its effects on memory. Pharmacology Biochemistry and Behavior, 1974, 2, 753-756.

Quartermain, D., & McEwen, B. S. Temporal characteristics of amnesia induced by protein synthesis inhibition: determination by shock level. Nature, 1970, 228, 667-678.

Quinton, E. E. Subamnesic cycloheximide treatment delays consolidation in mice. Journal of Comparative and Physiological Psychology, 1978, 92, 742-748.

Rainbow, T. C., Adler, J. E., & Flexner, L. B. Comparison in mice of the amnesic effects of cycloheximide and 6-hydroxydopamine in a one-trial passive avoidance task. Pharmacology Biochemistry and Behavior, 1976, 4, 347-349.

Randt, C. T., Barnett, B. M., McEwen, B. S., & Quartermain, D. Amnesic effects of cycloheximide on two strains of mice with different memory characteristics. Experimental Neurology, 1971, 30, 467-474.

Segal, D. S., Squire, L. R., & Barondes, S. H. Cycloheximide: its effects on activity are dissociable from its effects on memory. Science, 1971, 172, 82-84.

Squire, L. R. Short-term memory as a biological entity. In D. Deutsch & J. A. Deutsch (Eds.), Short-Term Memory. New York: Academic Press, 1975.

Squire, L. R., & Barondes, S. H. Anisomycin, like other inhibitors of cerebral protein synthesis, impairs 'long-term' memory of a discrimination task. Brain Research, 1974, 66, 301-308.

Squire, L. R., & Cohen, N. Remote memory, retrograde amnesia, and the neuropsychology of memory. In L. Cermak (Eds.), Memory and Amnesia. Hillsdale, NJ: Erlbaum, In press.

Squire, L. R., & Davis, H. P. The pharmacology or memory: a neurobiological perspective. Annual Review of Pharmacology and Toxicology, 1981, 21, In press.

Watts, M. E., & Mark, R. F. Drug inhibition of memory formation in chickens. II. Short term memory. Proceedings of the Royal Society (Series B: Biological Sciences, 1971, 178, 455-464.

Zornetzer, S. F., Abraham, W. C., & Appleton, R. The locus coeruleus and labile memory. Pharmacology Biochemistry and Behavior, 1978, 9, 227-234.

Footnotes

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Table 1

Median STLs (sec) Scored at Retention

Test of the Passive-Avoidance Habit

Test Time	ANI (1 mg/animal)	Saline
After Training		
0.5 hr	152.0	86.0
1.5 hr	211.5	207.0
3.0 hr	39.0*	300.0
6.0 hr	9.0**	300.0
1 day	23.0**	300.0
7 day	10.0**	300.0

*$p \leq 0.01$, **$p < 0.001$ as compared to saline-treated mice tested at the same time. N=25-28 per group.

Figure 1. Median STLs for mice tested at various times after training in Experiment 2. The different groups are represented as follows: ANI (1 mg/animal) x 1 ●——● ; Saline x 1 ●- - - - - - - ● ; ANI (1 mg/animal) x 2 ○——○ ; Saline x 2 ○- - - - - - - ○ ; ANI (1 mg/animal) x 3 ⊕——⊕ ; Saline x 3 ⊕- - - - - - - ⊕ . The N per point ranged between 25 and 28 for all groups except multiple injected mice tested at 1 or 7 days for which N=10 per group. *p<0.025, **p<0.01, ***p<0.001 as compared to corresponding saline controls.

Figure 2. Median STLs for mice tested at various times after training in Experiment 3. Experimental conditions are represented as follows: ANI (0.5 mg/animal) x 1 ●——● ; Saline x 1 ●- - - - - - - ● ; ANI (0.5 mg/animal) x 1 plus (2 mg/animal) ○——○ ; Saline x 2 ○- - - - - - - ○ ; ANI (0.5 mg/ animal) x 1 plus (2 mg/animal) x 2 ⊕——⊕ ; Saline x 3 ⊕- - - - - - - ⊕ . N=10 per group. *p<0.025, **p<0.001 as compared to corresponding saline controls.

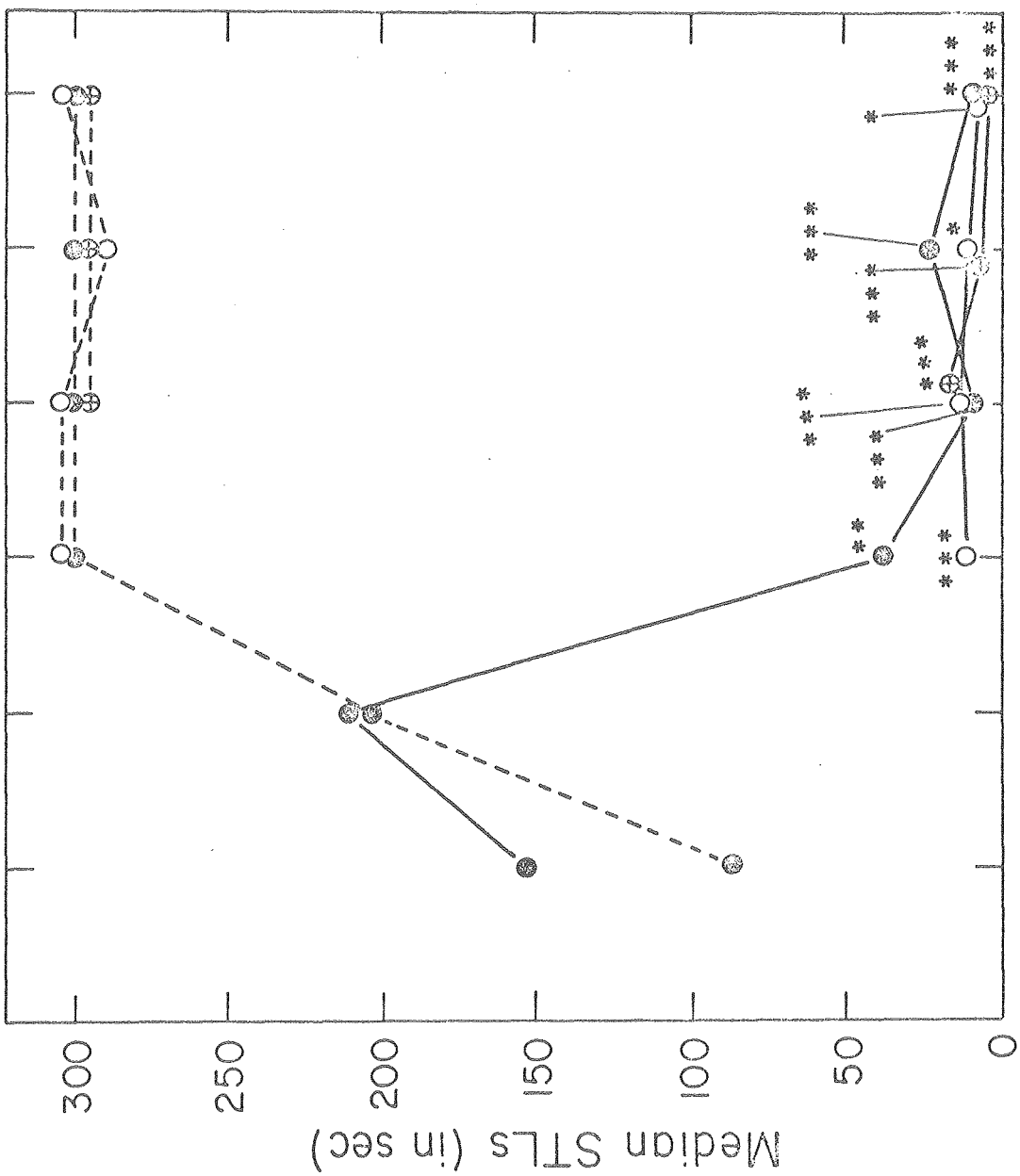

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Fig. 1

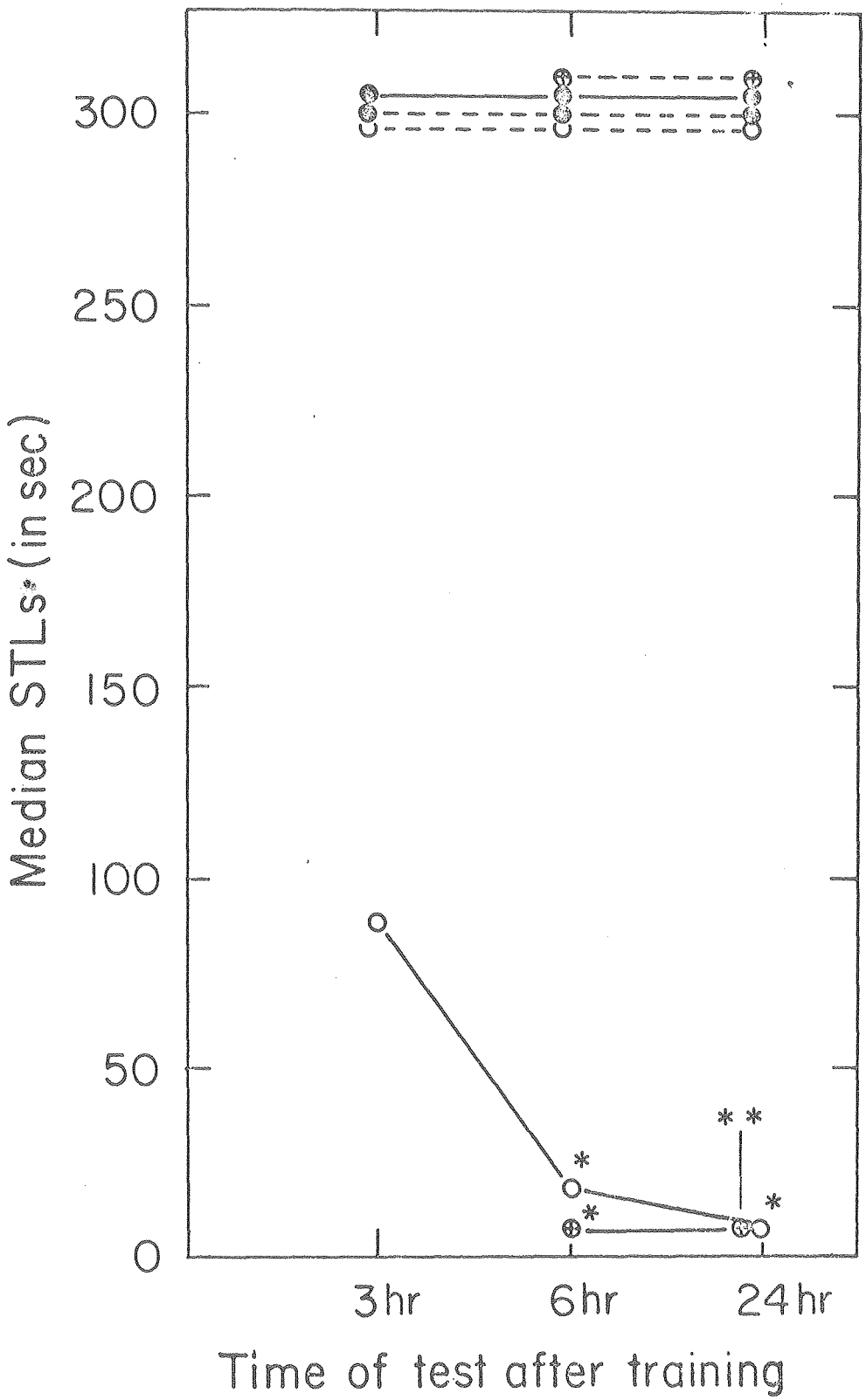

Fig. 2

XBL 809-4360